PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of early cryoprecipitate transfusion versus standard care in women who develop severe postpartum haemorrhage (ACROBAT) in the UK: A protocol for a pilot cluster randomised trial
AUTHORS	Green, Laura; Daru, Jahnavi; Dodds, Julie; Gonzalez Carreras, Francisco; Lanz, Doris; Zamora, Javier; Pardo Llorente, Maria del Carmen; Pérez, Teresa; Sweeney, Lorna; Thangaratinam, Shakila; Thomas, Amy; Khan, Khalid

VERSION 1 – REVIEW

REVIEWER	Keyvan Karkouti Toronto General Hospital Canada
REVIEW RETURNED	30-Dec-2019

GENERAL COMMENTS	This is a well-written protocol for a pilot cluster randomized trial comparing early cryoprecipitate therapy versus standard of care (late therapy) for PPH. Four institutions will be randomized, 2 to intervention and 2 to control. The study addresses an important clinical question, but I had several questions and comments. 1. The primary outcome is to assess the feasibility of administering cryo within 90 minutes of the first red cell unit request. Since the goal is to provide rapid fibrinogen supplementation, why not use fibrinogen concentrate rather than cryoprecipitate? There is no reason to expect that FC cannot be administered within 90 minutes of red cell request. If so, would a pilot study be needed at all? 2. I am not sure that a cluster randomized trial will be able to address the study question in the main trial. PPH occurs rarely, the presentation is quite variable, and I would suspect that the management will vary substantially across the different hospitals. It is noted that transfusion practice is highly protocolized at participating institutions, but no data is provided in support of this statement. It seems likely to me that between-hospital comparisons will lose any signal for all the noise. 3. Randomization (line 211): I am not sure how randomization by blocks works here. 4. Intervention (line 219): I am not sure that early fibrinogen therapy based solely on a single red cell transfusion is appropriate. How is active bleeding defined and how will it be confirmed? Is the fibrinogen level going to be measured prior (and after) therapy? If not, how will it be ensured that patients' fibrinogen levels are not too high prior to therapy? 5. Control group: When is fibrinogen level measured during standard of care therapy? Is it standardized?

	6. Ethics: Line 189-191 states that data will be collected on women who die or who are discharged before being identified. I can understand the rationale for the former group, but I am not sure whether the latter is ethically appropriate. If screening process is robust, then the latter should not occur. Can the blood bank not notify the research team every time a unit of red cells is requested for obstetrical patients? 7. What is the anticipated design for the definitive study? How many centres are anticipated to be needed? Will centres participating in this pilot study be excluded due to contamination? What results from this pilot trial would lead to a conclusion of feasibility for the main trial?

REVIEWER	Nicola Curry Oxford University Hospitals NHS Foundation Trust, Haematology
REVIEW RETURNED	31-Jan-2020

GENERAL COMMENTS	This is a paper describing the protocol of a pilot cluster randomised trial evaluating the feasibility of delivering cryoprecipitate within 90 minutes. THis is a well written paper, clearly setting out the protocol for the trial. I have few comments but set these out below: 1) Abstract: the authors comment that this is the first study to evaluate early fibrinogen replacement in PPH. I think it would be worth adjusting this wording, as the OBS2 trial - although different - did evaluate the effects of fibrinogen therapy in PPH and it was given fairly rapidly after a ROTEM result. This comment applies to the strengths/weaknesses section too. 2) control group vs intervention group: the intervention group will be all patients who have PPH in the 2 hospitals allocated to this arm. IN the control group the patients will only get cryo if the Fg falls below 2g/L or have a MT. I wonder how the authors plan to compare these groups with regard to outcome, as they will not be the same patients. It is known that some women with PPH do not drop their Fg levels early, whereas others do, and I would wonder if the secondary outcomes will be affected by this. I would like to understand how the authors plan to address this likely difference. 3) I think the inclusion of qualitative data collection from participants - on how they feel about the intervention - is a great addition to this protocol. This is a clearly well thought out study and I look forward to the results.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
1. "The primary outcome is to assess the feasibility of administering cryo within 90 minutes of the first red cell unit request. Since the goal is to provide rapid fibrinogen supplementation, why not use fibrinogen concentrate rather than cryoprecipitate? There is no reason to expect that FC cannot be administered within 90 minutes of red cell request. If so, would a pilot study be needed at all?"

In the UK cryoprecipitate is the main fibrinogen replacement therapy, rather than fibrinogen concentrate, which is why we chose cryoprecipitate as our intervention. Taking into consideration the

transport time and the ~20 - 30min thawing times required for cryoprecipitate prior to its use, we wanted to test if it is feasible to administer cryoprecipitate early.

Even in the case of fibrinogen concentrate, one pilot randomised control trial in trauma showed that it was not feasible to administer fibrinogen concentrate within 45 minutes of hospital admission: in this study only 69% of patients received the intervention early (Curry N et. Al. Crit Care. 2018 Jun 18;22(1):164).

Thus, it is important that prior to launching a large trial for fibrinogen replacement therapies, we should assess the feasibility of administering this intervention early.

2. "I am not sure that a cluster randomized trial will be able to address the study question in the main trial. PPH occurs rarely, the presentation is quite variable, and I would suspect that the management will vary substantially across the different hospitals. It is noted that transfusion practice is highly protocolized at participating institutions, but no data is provided in support of this statement. It seems likely to me that between-hospital comparisons will lose any signal for all the noise."

This is a good point raised by the reviewer, and it remains unanswered if cluster or individualised randomisation in this setting is better, considering the frequency of PPH.

Prior to deciding on the design of the current trial, the input we obtained from obstetricians and anaesthetists dealing with the PPH was that a cluster design would be better, because PPH occurs rarely and thus clinicians are likely to forget to randomise women when bleeding occurs. The cluster design, however, would also allow for the integration of the intervention into routine care, and thus provide a better chance of success for administering intervention.

The design of the main trial is likely to be the same, with hospitals nested within treatment groups. Therefore, the effect of treatments should be estimated using the appropriate adjusted test for cluster-randomised trials.

Prior to initiating this study, we also assessed transfusion major haemorrhage protocols on all sites, and these were comparable and in line with the national guidelines. A comment reflecting this has been added in the discussion (lines 368-370).

3. "Randomization (line 211): I am not sure how randomization by blocks works here."

Thank you for this comment. This was intended to emphasise that we sought to avoid an imbalance in allocation by predefining the maximum number of allocations per arm.
However, since that the ratio of 1:1 is already given, we agree this is an overemphasis and we have amended the corresponding lines.

4. "Intervention (line 219): I am not sure that early fibrinogen therapy based solely on a single red cell transfusion is appropriate. How is active bleeding defined and how will it be confirmed? Is the fibrinogen level going to be measured prior (and after) therapy? If not, how will it be ensured that patients' fibrinogen levels are not too high prior to therapy?"

The criteria for administering the intervention (see primary objective) is any woman who is actively bleeding and for whom clinician requests blood transfusion to treat the bleeding. Red blood cell is always the first to be requested followed by plasma transfusion).

Fibrinogen levels will be measured as part of routine care: however, its levels will not be used to determine administration of intervention, as we know that there is a delay in obtaining blood results. In this study we have hypothesised that a more proactive approach to correcting fibrinogen in women who develop PPH and who require blood transfusion, will pre-empt hypofibrinogenemia, and thus optimise haemostasis earlier, resulting in improved outcomes for women. This has been justified in the introduction section.

5. "Control group: When is fibrinogen level measured during standard of care therapy? Is it standardized?"

We expect hospitals to follow national guidelines that recommend 'serial haemostatic tests, including platelet count, PT, APTT and fibrinogen, from before and after resuscitation should be used regularly, every 30–60 min depending on the severity of the haemorrhage, to guide and ensure the appropriate use of haemostatic blood components (BSH guideline on Major Haemorrhage, Br J Haematol. 2015 Sep;170(6):788-803).

Since this is a pragmatic trial, we did not change the clinical practice and thus did not ask for additional blood samples during PPH. Fibrinogen results that have been collected as part of routine care will be reported in this study.

6. "Ethics: Line 189-191 states that data will be collected on women who die or who are discharged before being identified. I can understand the rationale for the former group, but I am not sure whether the latter is ethically appropriate. If screening process is robust, then the latter should not occur. Can the blood bank not notify the research team every time a unit of red cells is requested for obstetrical patients?"

The instances when women are discharged from hospitals before being identified are mainly on the weekend when the research team are not available to approach women for consent.

For these cases women will still be contacted by the research team after discharge where they will have the opportunity to consent or refuse consent for the data collection.

The routine de-identified data collection will only occur for cases where the research team has been unable to get hold of women on three separate occasions. For this we have obtained approval from confidentiality advisory group (CAG), and Health Research Authority (CAG reference: 18/CAG/0199 IRAS project ID: 237959 REC reference: 18/LO/2062).

In the manuscript (line 195) we have made it clear that this is only for women 'who are discharged from hospital before being identified and approached for their consent and who cannot be contacted after discharge…'

7. "What is the anticipated design for the definitive study? How many centres are anticipated to be needed? Will centres participating in this pilot study be excluded due to contamination? What results from this pilot trial would lead to a conclusion of feasibility for the main trial?"

The anticipated design will be the same as this trial, if we demonstrate that it is feasible to administer cryoprecipitate early in the intervention arm and as per current national guideline in the control arm.

We don't know how many centres will participate at this stage, as this will depend on the primary outcome we choose for the large trial. This will be determined from the results of the pilot study (i.e. assessing which outcomes are occurring after the intervention) as well as the input from clinicians and patient representatives which we are collecting alongside the pilot study. We have included this in the discussion section (final paragraph).

After the pilot study, all centres will go back to current standard protocol. Prior to the large trial, these centres will be assessed to ensure that there is no contamination. If they are not administering early cryoprecipitate, then they will be invited to take part in the large trial, but if they are, then they will be excluded.

The trial has 3 variables to determine if it is feasible to proceed with the large trial, these are consent rate, proportion of women who receive intervention in accordance with the allocated treatment, and the proportion of women for whom clinical data is obtained. A table giving criteria for each of these variables is now added to the manuscript (Table 2).

Reviewer 2:
1) "Abstract: the authors comment that this is the first study to evaluate early fibrinogen replacement in PPH. I think it would be worth adjusting this wording, as the OBS2 trial - although different - did evaluate the effects of fibrinogen therapy in PPH and it was given fairly rapidly after a ROTEM result. This comment applies to the strengths/weaknesses section too."

In the abstract, strengths and limitations and discussion sections, we have corrected this to say that this is the first study to evaluate early cryoprecipitate transfusion in PPH.

Due to word limit, we are unable to expand on other fibrinogen concentrate trials in PPH in this manuscript. However, we have recently published a systematic review addressing the evidence of early use of fibrinogen replacement therapy in PPH where we have analysed the OBS-2 trial in detail (Zaidi A et. al. Early Use of Fibrinogen Replacement Therapy in Postpartum Hemorrhage-A Systematic Review. Transfus Med Rev. 2020 Jan 28. pii: S0887-7963(20)30009-2). We have added this reference to the discussion.

2) "control group vs intervention group: the intervention group will be all patients who have PPH in the 2 hospitals allocated to this arm. IN the control group the patients will only get cryo if the Fg falls below 2g/L or have a MT. I wonder how the authors plan to compare these groups with regard to outcome, as they will not be the same patients. It is known that some women with PPH do not drop their Fg levels early, whereas others do, and I would wonder if the secondary outcomes will be affected by this. I would like to understand how the authors plan to address this likely difference."

We agree with the reviewer that fibrinogen level in the intervention arm is likely to be higher compared with the control arm at the end of PPH treatment. However, comparisons of fibrinogen levels are not part of the secondary analysis, and this will only be reported in this study if it has been tested as part of routine care. Further, the study is not powered to assess any differences in other clinical outcomes, and hence all these will be reported as descriptive data in the final analysis.

The main secondary outcomes of the study are to assess the completeness of the clinical data and the acceptability of the study by women and healthcare professionals.

3) "I think the inclusion of qualitative data collection from participants - on how they feel about the intervention - is a great addition to this protocol."

Thank you for this comment.

VERSION 2 – REVIEW

REVIEWER	Keyvan Karkouti University of Toronto, Canada.
REVIEW RETURNED	15-Apr-2020

GENERAL COMMENTS	Thank for you answering the issues raised. I have no further questions.

REVIEWER	Nicola Curry Oxford University Hospitals NHS Foundation Trust, Haematology
REVIEW RETURNED	06-Apr-2020

GENERAL COMMENTS	This is a protocol for a cluster randomised pilot trial evaluating the feasibility of cryoprecipitate in the treatment of post partum haemorrhage. The authors have addressed all of my previous comments and I have no additional comments to make. Thank you.